2018-03-06

Long-term outcomes of on vs. off pump coronary artery bypass grafting

Smart, N

10.1016/j.jacc.2017.12.049
Journal of the American College of Cardiology
Elsevier

Long-term outcomes of on vs. off pump coronary artery bypass grafting

Neil A. Smart PhD[1], Gudrun Dieberg PhD[1], & Nicola King PhD[2]

1. School of Science and Technology, University of New England.

2. School of Biomedical and Healthcare Sciences, Plymouth University Peninsula Schools of Medicine and Dentistry, University of Plymouth, Plymouth, PL4 8AA, UK.

Address for Correspondence: School of Biomedical and Healthcare Sciences

Plymouth University Peninsula School of Medicine and Dentistry

University of Plymouth

Plymouth, PL4 8AA, UK.

Tel: +44 1752 584969

Fax: +44 1752 586788

e-mail: nicola.king@plymouth.ac.uk

Funding source: none

Conflicts of interest: none declared

Acknowledgments: none

Running head: long-term clinical outcomes after on- vs off-pump CABG

Word Count: 3

ABSTRACT

Background: It is important, when comparing effects of on vs. off pump coronary artery bypass grafting, to assess the long-term clinical outcomes. However, most research conducted thus far has concentrated on short-term outcomes and ignored the long-term clinical outcomes, especially the 5-year outcomes of the largest randomised controlled trials.

Objectives: The aim of this systematic review and meta-analysis is to investigate the long-term clinical outcomes of on vs. off pump CABG.

Methods: To identify potential studies systematic searches were carried out using various databases. The search strategy included the key concepts of "cardiopulmonary bypass" AND "off pump" AND "long term" OR "5 year outcomes". This was followed by a meta-analysis investigating mortality, incidence of myocardial infarction (MI), incidence of angina, need for revascularisation, and incidence of stroke.

Results: Six studies totalling 8145 participants were analysed. In the on pump group mortality was 12.3% compared to 13.9% in the off pump group. The odds ratio (OR) for this comparison was 1.16 (95% confidence interval [CI] 1.02, 1.32; p=0.03). In contrast, there were no differences in the incidence of MI: OR 1.06 (95% CI 0.91, 1.25; p=0.45; 8.4 vs. 7.9%); incidence of angina: OR 1.09 (95% CI 0.75, 1.57; p=0.65; 2.3 vs. 2.1%); need for revascularisation OR 1.15 (95% CI 0.95, 1.40; p=0.16; 5.9 vs. 5.1%); and the incidence of stroke OR 0.78 (95% CI 0.56, 1.1; p=0.16; 2.2 vs. 2.8%).

Conclusions: Statistically on pump CABG appeared to offer superior long term survival, although the clinical significance of this maybe more uncertain.

Keywords: long term clinical outcomes; on pump; off pump; CABG

Abbreviations

BHACAS: beatin heart against cardioplegic arrest study

CABG: Coronary artery bypass grafting

CENTRAL: Cochrane central registry of controlled trials

CPB: Cardiopulmonary bypass

MI: Myocardial infarction

OR: Odds Ratio

RCT: Randomised controlled trial

CONDENSED ABSTRACT

Clinical decision makers choosing whether to perform coronary artery bypass grafting (CABG) on or off pump must consider the long-term clinical outcomes. This systematic review and meta-analysis was the first to consider those long-term clinical outcomes using only results from randomised clinical trials and including the largest clinical trials to date. Statistically, the results showed that compared to off pump CABG on pump CABG conferred a long-term survival benefit, although this may not translate into clinical significance. There was no difference in the incidence of myocardial infarction, angina, stroke or the need for revascularisation.

INTRODUCTION

First introduced in the mid 1960s coronary artery bypass grafting (CABG) is the gold standard treatment for patients with extensive coronary artery disease [1]. The first successful open heart operation using cardiopulmonary bypass (CPB) was carried out in 1952 [2]. The development and success of this approach has undoubtedly contributed to the decline in deaths due to coronary artery disease that has occurred in developed countries during the last 5 decades [1]. However, coronary revascularisation on CPB with its attendant aortic manipulation has been implicated in various complications including increased risk of stroke [3, 4] and stimulation of a systemic inflammatory response [5]. This led in the mid 1980s to renewed interest in performing CABG on the beating heart [6] helped by the development of various stabilising devices [7], in spite of the increased difficulty of this approach [5]. Since that time there has been ongoing debate as to which technique is superior including several meta-analyses that have not fully answered the question [3-4, 8-9]. A good illustration of the dichotomy is the fact that 95% of CABGs in India are performed off pump [5], whereas the figure in the UK is about 20% [10].

The most important factor governing the choice of whether to go on or off pump is the long-term outcomes. Until now, these have been difficult to assess due to the sparsity of long-term reporting from randomised controlled trials (RCTs). Some resolution to this problem has recently occurred with the publication of the 5-year outcomes of two of the largest RCTs to date, namely ROOBY [11] and CORONARY [12]. Therefore, the aim of this systematic review was to synthesise the results from all studies reporting the long-term (> 4 years) clinical outcome of RCTs that investigated on vs off pump CABG. This is the first meta-analysis to only consider long-term results from RCTs and to include the results from ROOBY and CORONARY.

METHODS

Search strategy

To identify potential studies systematic searches were carried out using the following databases: EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of "cardiopulmonary bypass" AND "coronary artery bypass grafting" AND "off pump" AND "long term" OR "5 year outcomes". All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until September 1st, 2017.

Types of studies to be included

This meta-analysis only included studies reporting long-term (> 4 years) outcomes from RCTs of off pump vs. on pump in patients undergoing CABG. There were no language restrictions. Animal studies, review papers and non-randomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or participants who were treated by other modalities such as percutaneous coronary intervention were excluded. Incomplete data was excluded. Studies that included interventions other than off pump vs. on pump CABG were excluded.

Participants/population

Only studies reporting the long-term outcomes (> 4 years) of RCTs of both male and female adult (≥18 years) patients with coronary artery disease who were undergoing CABG using either off or on pump were included.

Intervention(s), exposure(s)

This meta-analysis considered all studies reporting the long-term (> 4 years) outcomes from RCTs where patients with stable angina or acute coronary syndrome being treated with CABG were exposed to either on pump or off pump. More specifically, all long-term (> 4 years) studies directly derived from RCTs where the intervention of carrying out CABG without the use of cardiopulmonary bypass.

Comparator(s)/control

The studies in this analysis compared the long-term outcomes of off pump CABG with a usual care control group receiving on pump CABG.

Search Results

Our initial search found 204 articles. The majority Of these studies were excluded on the basis they were not RCTs. Four studies were excluded because they were retrospective analyses, 4 studies were excluded because they only reported short-term outcomes, 1 study was excluded as it had no comparator group and 1 study was excluded as it duplicated data (see supplementary Figure S1). Six studies were included in our analysis.

Outcome(s)

The primary outcomes analysed were: mortality, incidence of MI, angina, requirement for revascularisation, incidence of stroke and quality of life.

Risk of bias (quality) assessment

Risk of bias was assessed using a modification of the JADAD scale [13].

Strategy for data synthesis

Odds ratios were calculated for dichotomous data. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. All analyses were conducted using Revman 5.3 (Nordic Cochrane Centre, Denmark). A fixed effects inverse variance model was used throughout. Heterogeneity was quantified using the Cochrane Q test [14]. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

RESULTS

The 6 studies [10, 12-13, 15-17] included in the analyses had an aggregate of 8,145 participants, 4,069 of which had on pump CABG and 4,076 had off pump CABG. Table 1 summarises the characteristics of the included studies. Supplementary Table S2 lists the excluded RCTs and reasons for exclusion. Angelini et al [10] reported the clinical outcomes at > 4 years, whereas the remainder of studies reported outcomes at 5 years [12-13, 15-17].

Mortality

All of the studies reported the incidence of mortality. In total 568 / 4074 patients (13.9%) of the off pump patients had died at follow up compared to only 500 / 4068 (12.3%) of the on pump patients. The Odds Ratio (OR) for the comparison was 1.16 [95% Confidence Interval (CI) 1.02, 1.32; $I^2 = 49\%$; Z = 2.22; p = 0.03] (Figure 1a). The odds of dying was significantly greater in the off pump group compared to the odds of dying in the on pump group. The Funnel plot was symmetrical (Figure 1b).

Myocardial infarction incidence

Five studies reported the incidence of myocardial infarction (MI). In total 333 / 3976 (8.4%) patients had an MI in the off pump group compared to 314 / 3969 (7.9%) in the on pump group. The OR was 1.06 [95% CI 0.91, 1.25; $I^2 = 50\%$; Z = 0.76; p = 0.45] (Figure 2a). There was no significant difference in the odds of having an MI between the two groups. The funnel plot was symmetrical (Figure 2b).

Angina incidence

Three studies reported the incidence of angina. In total 62 / 2731 (2.3%) of off pump patients were experiencing angina compared to 57 / 2730 (2.1%) of the on pump patients. The OR was 1.09 [95% CI 0.75, 1.57; $I^2 = 54\%$; Z = 0.45; p = 0.65] (Figure 3a). The likelihood that patients were experiencing angina was similar in each group. The funnel plot was symmetrical (Figure 3b).

Requirement for revascularisation

Five studies reported the need for revascularisation. In total 233 / 3976 (5.9%) of the off pump patients required revascularisation compared to 204 / 3969 (5.1%) of the on pump patients. The OR was 1.15 [95% CI 0.95, 1.4; I^2 = 0%, Z = 1.41; p = 0.16] (Figure 4a). There was no significant difference in the odds of requiring revascularisation between each group. The funnel plot was symmetrical (Figure 4b)

Stroke incidence

Three studies reported the incidence of stroke. In total 60 / 2672 (2.2%) of off pump patients had a stroke compared to 76 / 2669 (2.8%) of the on pump group. The OR was 0.78 [95% CI 0.56, 1.1; I^2 = 0%; Z = 1.39; p = 0.16] (Figure 5a). There was no significant difference in the odds of a stroke occurring in the off pump group as in the on pump group. The funnel plot was symmetrical (Figure 5b).

Study Quality

The modified Jadad scale of study quality revealed a median score of 3.5 (table S2). The quality of the studies varied from a low score of 2 to a high score of 4. Over 50% of the studies described the method of randomisation; however, no studies described the method of blinding for which it should be noted that it is impossible to blind the surgeon as to whether (s)he is performing off or on pump CABG.

DISCUSSION

This is the first meta-analysis to consider the long-term (> 4 years follow up) clinical effects of on vs. off pump CABG using only RCTs and including the 5-year outcomes of two of the largest RCTs to date [11-12]. The results presented here suggest that there is a significantly lower mortality incidence in the on pump group, whereas the incidence of MI, angina, revascularisation and stroke were similar in both groups.

Meta-analyses pool results from all included without focussing on one trial over another. With the exception of Puskas et al [17], all of the RCTs included had higher rates of mortality in the off pump group; however, only in the case of the ROOBY trial did this reach significance. It has been suggested that this might be due to differences in the surgeons' experience. The CORONARY trial [12] demanded that all of the surgeons had at least 2 years' experience of performing off pump CABG, whilst the ROOBY trial only required surgeons to have experience of 120 cases (median 50) [11].

This meta-analysis concentrated on prospective RCTs; however there been other large retrospective studies that have investigated long term survival. On the whole, these studies have shown no difference in mortality between off pump and on pump CABG [18]. In the 2 exceptions long-term survival rates were significantly better in the on pump group. This bears some similarities to the current meta-analysis where individual studies showed no differences in survival but the overall mortality was statistically in favour of the on pump group, although whether the absolute difference is of clinical significance maybe more uncertain.Two of the factors that could contribute to long-term outcomes are graft patency and completeness of revascularisation. Related to this are concerns that performing CABG off pump means that distal anastomoses are performed on the beating heart [9]. These disquiets appeared to be

supported by the short-term outcomes of the CORONARY and ROOBY trials, which showed lower graft patency and higher rates of revascularisation in the off pump group [20-21]. It is therefore noteworthy that at 5-years neither MI, angina nor revascularisation were significantly different in the two groups. In accordance with this Angelini et al. [10] and Puskas et al. [17] specifically studied graft patency at > 4 years and found there to be no difference.

The incidence of stroke following CABG is approximately 2.0-3.7% [22-23], where the 5-year outcomes of the SYNTAX trial showed the incidence of stroke to be insignificantly different between CABG and PCI [23]. This meta-analysis concentrated on long-term clinical outcomes, which showed there to be no difference in the incidence of stroke between the two groups. A recent network meta-analysis showed that avoiding aortic manipulation in the off pump group significantly reduced the incidence of stroke at 30 days [19]. A lower incidence of stroke in the off pump group at 30 days was also found in two of the recent meta-analyses [3, 4], although the third found no difference [8].

Limitations

Myocardial protection during on pump CABG varied between studies. For instance whilst Angelini et al [24] and Puskas et al [7] used hyperkalaemic warm blood cardioplegia, Hueb et al used cold crystalloid cardioplegia [16]. The majority of the studies used the Octopus stabiliser.

The median study quality score was moderate with studies scoring between 2-4 on a scale of 6. There was also some evidence of heterogeneity in a number of the analyses. It should be noted though that the funnel plots were all symmetrical.

It is impossible to blind the surgeon as to which type of surgery they are to perform. However, not all studies reported the method of randomisation and described withdrawals and dropouts. This would be something that future studies may like to take into account.

Conclusion

After > 4 years of follow up off pump CABG was associated with higher all cause mortality compared to on pump CABG. All other comparisons including revascularisation, MI and angina were insignificantly different.

PERSPECTIVES

Competency in Medical Knowledge 1: Selection of whether to perform coronary artery bypass grafting on or off pump must consider the long-term clinical outcomes as well as patient's preferences.

Competency in Medical Knowledge 2: Statistically on pump CABG offers superior long term survival, although clinically this outcome is less certain.

Competency in Patient Care: In terms of long term survival on pump CABG is non inferior compared to off pump CABG.

Competency in Interpersonal & Communication Skills: It is important to discuss the short- and long-term clinical outcomes of on or off pump surgery with patients who are about to undergo CABG.

Translational Outlook 1: Although several of the long term clinical outcomes of on vs off pump were similar, there did appear to be a survival advantage with on pump CABG.

Translational Outlook 2: Ideally more studies investigating the long term outcomes of randomised controlled trials comparing on vs off pump CABG are needed.

REFERENCES

1. Head SJ, Börgerman J, Osnabrugge RLJ et al. Coronary artery bypass grafting: part 2 – optimizing outcomes and future prospects. Eur Heart J 2.13;34:2873-86.
2. Šušak S, Redžek A, Rosić M, Velicki L, Okilijević B. Development of cardiopulmonary bypass – a historical review. Srp Arh Celok Lek 2016;144:670-5.
3. Deppe A-C, Arbash W, Kuhn EW et al. Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16 900 patients investigated in randomized controlled trials. Eur J Cardio-thoracic Surg 2016;49:1031-41.
4. Kowalewski M, Pawliszak W, Giorgio P et al. Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients compared with on-pump coronary artery bypass grafting: meta-analysis. J Thorac Cardiovasc Surg 2016;151:60-77.

5. Apostolakis E, Papakonstantinou NA, Koniari I. Myocardial revascularization without extracorporeal circulation; why hasn't it convinced yet? Ann Card Anaesth 2017;20:219-225.
6. Gundry SR, Romano MA, Shattuck OH, Razzouk AJ, Bailey LL. Seven-year follow-up of coronary artery bypasses performed with and without cardiopulmonary bypass. J Thorac Cardiovasc Surg 1998;115:1273-8.
7. Puskas JD, Williams WH, Duke PG et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:797-808.
8. Dieberg G, Smart NA, King N. On- vs. off-pump coronary artery bypass grafting: a systematic review and meta-analysis. Int J Cardiol 2016;223:201-11.
9. Møller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database of Systematic Rev 2012:CD007224.
10. Angelini GD, Culliford L, Smith DK et al. Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: long term follow-up of 2 randomized controlled trials. J Thorac Cardiovasc Surg 2009;137:295-303.
11. Shroyer AL, Hattler B, Wgner TH et al. Five-year outcomes after on-upmp and off-pump coronary-artery bypass. N Eng J Med 2017;377:623-32.
12. Lamy A, Devereaux PJ, Prabhakaran D et al. Fiev-year outcomes after off-pump or on-pump coronary-artery bypass grafting. N Eng J Med 2016;375:2359-68.

13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: Assessing the Quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
14. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al: The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *Br Med J*. 2011;343:d5928.
15. van Dijk D, Spoor M, Hijman R et al. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. J Am Med Assoc 2007;297:701-8.
16. Hueb W, Lopes NH, Pereira AC et al. Five-year follow-up of a randomized comparison between off-pump and on-pump stable multivessel coronary artery bypass grafting. The MASS III trial. Circ 2010;122[suppl 1]:S48-S52.
17. Puskas JD, Williams WH, O'Donnell R et al. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. Ann Thorac Surg 2011;91:1836-43.
18. Chivasso P, Guida GA, Fudulu D et al. Impact of off-pump coronary artery bypass grafting on survival: current best available evidence. J Thorac Dis 2016;8(suppl 10):S808-S817).
19. Zhao DF, Edelman JJ, Seco M et al. Coronary artery bypass grafting with and without manipulation of the ascending aorta. J Am Coll Cardiol 2017;69:924-936.
20. Lamy A, Devereaux PJ, Prabhakaran D et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Eng J Med 2013;368:1179-88.
21. Shroyer AL, Grover FL, Hattler B et al. On-pump versus off-pump coronary-artery bypass surgery. N Eng J Med 2009;361:182-37.

22. Anyanwu AC, Filsoufi F, Salzberg SP, Bronster DJ, Adams DH. Epidemiology of stroke after cardiac surgery in the current era. J Thorac Cardiovasc Surg 2007;134:1121-7.
23. Mohr FW, Morice M-C, Kappetein MAP et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.
24. Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in beating heart against cardioplegia arrest studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 2002;359:1194-9.

FIGURES AND TABLES

Central Figure: Forrest plot of the incidence of mortality. This shows that the odds of mortality occurrence were significantly greater in the off pump group compared to the on pump group. Summary statistics for each study are shown in the table on the left with each study's odds ratio (square) and 95% confidence interval (whiskers) plotted on the right. Underneath the table is the overall statistic.

Figure 1: Mortality incidence. 1a Forest plot. The table summarises each study, whilst the graph plots each study's odds ratio (blue squares with the black whiskers indicating 95% confidence intervals) and the overall odds ratio (black diamond, the centre of which indicates the overall odd ratio, whilst the width of the diamond indicates the 95% confidence interval). The overall statistics are shown beneath the table. 1b Funnel plot, which plots the odds ratio for each study against the standard error of the odds ratio.

Figure 2: Incidence of myocardial infarction. 2a Forest plot showing that the odds for myocardial infarction occurring were similar in the off and on pump groups. All other details as Figure 1a. 2b Funnel plot. All details as Figure 1b.

Figure 3: Incidence of angina. 3a Forest plot showing that the odds of angina occurring were similar in the off and on pump groups. All other details as Figure 1a. 3b Funnel plot. All details as Figure 1b.

Figure 4: Need for revascularization. 4a Forest plot showing that the odds for requiring revascularisation were similar in the off and on pump groups. All other details as Figure 1a. 4b Funnel plot. All details as Figure 1b.

Figure 5: Incidence of stroke. 5a Forest plot showing that the odds for the incidence of stroke were similar in the off and on pump groups. All other details as Figure 1a. 5b Funnel plot. All details as Figure 1b.

Table 1: Characteristics of included trials. Table showing the basic features of the included trials including: the number of patients in each group; the mean age of the patients in each group; the number of years of follow up; the percentage of male patients in each group; and, the outcomes measured in each trial. BHACAS: beating heart against cardioplegic arrest study; MI: myocardial infarction.

Table 1 – Included studies

Study	N OnCPB (OffCPB)	Age OnCPB (OffCPB)	Years of follow-up	Male % OnCPB (OffCPB)	All outcome measures
Angelini et al. 2009 [10] England	BHACAS 1: 100 (100) BHACAS 2: 101 (100)	BHACAS 1: 61.7 ± 8.6 (62.2 ± 9.6) BHACAS 2: 61.2 ± 9.2 (63.8 ± 8.5)	> 4 > 4	BHACAS 1: 79 (82) BHACAS 2: 85 (82)	Angina Graft patency MI Mortality Quality of life Revascularisation
Van Dijk et al. 2007 [15] Netherlands	139 (142)	60.8 ± 8.8 (61.7 ± 9.2)	5	70.5 (66.2)	Cognitive outcomes MI Mortality Quality of life Revascularisation Stroke
Hueb et al. 2010 [16] Brazil	155 (156)	59 (61)	5	80 (78)	Angina MI Mortality Positive treadmill test Revascularisation Stroke
Lamy et al. (2016) [12] USA	2377 (2375)	67.5 ± 6.9 (67.6 ± 6.7)	5	81.7 (80)	Angina Costs per patient MI Mortality New renal failure Quality of life

					Revascularization Stroke
Puskas et al. (2011) [17] USA	99 (98)	62.2 ± 11.1 (62.5 ± 9.5)	5	77 (78)	Graft patency Mortality
Shroyer et al. (2017) [11] USA	1099 (1104)	64 ± 11 (68 ± 9)	5	62.5 ± 8.5 (63.0 ± 8.0)	MI Mortality Revascularization